

Review Article

Potential biomarkers of Poly (ADP-ribose) polymerase inhibitors for cancer therapy

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Abstract: As Olaparib has received FDA-approval for treatment of cancer patients with BRCA1 and BRCA2 mutations, the target related on Poly (ADP-ribose) polymerase (PARP) inhibitors have been emerging as a novel therapy for treatment of patients with advanced ovarian cancer. It has been observed that PARP inhibitors have optimistic antitumor activity of patients in advanced ovarian cancer bearing homologous recombination (HR) defects, supporting a substantially wider role for PARPi. Strategies to identify other potential biomarkers remain under investigation. Herein, we review recent updates on potential molecular markers to predict biomarker of PARPi for cancer therapy and proposed an integrated biomarker system to predict the “appropriate users” of PARPi. It may help overcome PARPi treatment failure, which reveal novel insights into clinical use of PARPi.

Keywords: PARP, BRCA, biomarker

Poly (ADP-ribose) polymerase-1 (PARP1) is an enzyme involved in DNA repair that utilizes NAD⁺ as a substrate to catalyze ADP-ribose polymers on target proteins once DNA nick occurs [1]. PARP1 has experienced a rapid development since its discovery in 1963 by Paul Mandel's team [2]. After 50 years discovery of PARP inhibitors (PARPi), it has entered clinical trial [3] and become a potential drug in anti-cancer therapy. The first PARP inhibitor Olaparib has been granted a marketing authorization by FDA for treatment of cancer patients with BRCA1 and BRCA2 mutation in 2014. Persistent single strand break (SSB) interrupted by PARPi and double strand break (DSB) mediated by BRCA-associated deficiency exist the same time was defined as synthetic lethal strategy [4]. Clinical trials of PARPi have evaluated their effectiveness used as monotherapy in treating ovarian or breast cancer with BRCA1 or BRCA2 mutation [5, 6]. PARPi can also be

used in combination with chemotherapy, such as temozolomide [7], cyclophosphamide [8], topotecan [9], paclitaxel [10], cisplatin [11], gemcitabine [11], and irinotecan [12].

To date, the leading indication of PARPi in clinical trials [13, 14] is tumors that developed in patients with mutations in BRCA1/2 gene. However, multiple publications proposed the PARPi resistance in BRCA1/2 mutation carriers [15, 16]. What is more, restricting PARPi research to BRCA1/2 mutation would exclude additional cancer patients who may benefit. The challenge remains to develop an effective strategy to predict the biomarkers such that the patient population who are more likely to response to PARPi therapy may be identified. Our review addresses recent updates on biomarkers that are benefit for tumor carriers to get PARPi treatment and propose an integrated biomarker system to predict the “appropriate users” of PARPi.

Biomarkers of PARPi for cancer therapy

Table 1. Clinical Trial of PARP inhibitors

PARPi	Company	Efficiency of PARPi (IC ₅₀)	Clinical Trial	Reference
Olaparib	AstraZeneca	4.9 nM (PARP1)	I/II/III	Chen Y et al. 2013 [18]
Veliparib	Abbott	5.2 nM (PARP1) 2.9 nM (PARP2)	I/II/III	Michel J et al. 2013 [20]
BMN 673	BioMarin	1.98 nM (PARP1)	I/II/III	Wang B et al. 2016 [19]
Rucaparib	Clovis	1.4 nM (PARP1)	I/II	
CEP-9722	Cephalon	20 nM (PARP1) 6 nM (PARP2)	I/II	Plummer R et al. 2015 [21]
Niraparib	TesaroBio	3.8 nM (PARP1) 2.1 nM (PARP2)	I/II/III	Jones P et al. 2015 [22]

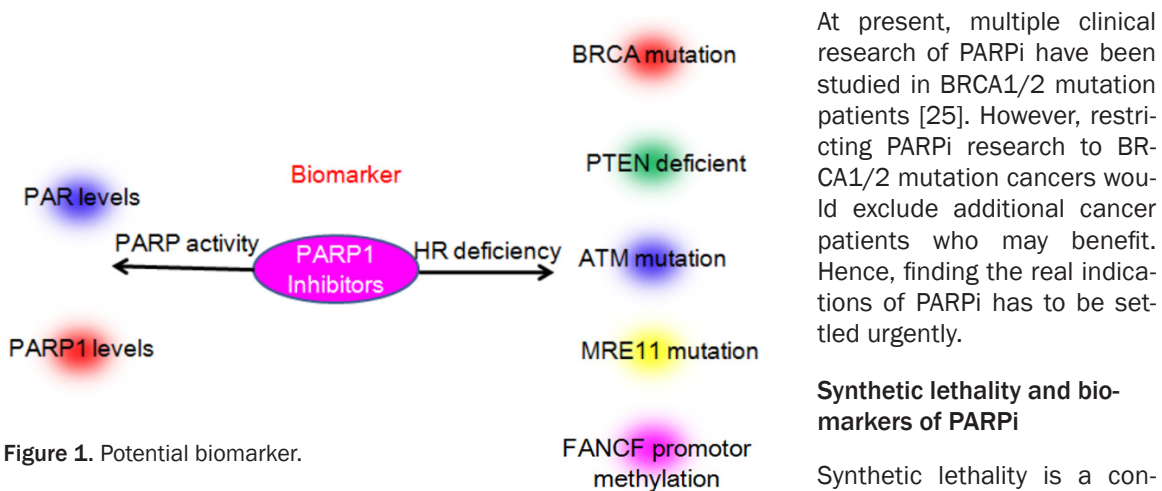


Figure 1. Potential biomarker.

Clinical trial of PARP inhibitors

The development of PARPi has progressed greatly over the last few years. However, due to the failed trial for triple negative breast cancer in 2012, Iniparib was dropped by Sanofi-Aventis. It has not impeded the development of PARPi. Soon, it is confirmed that Iniparib is not a bona fide PARPi [17]. After several years ups and downs, multiple PARP inhibitors are in clinical trial as monotherapy agents or in combination therapy agents now. There are at least 6 PARP inhibitors under clinical trial (Table 1 [18-22]).

Olaparib has been the PARP inhibitor granted a marketing authorization by both European Medicines Agency [23] and FDA [24] in patients with advanced ovarian cancer caused by a mutated BRCA gene or BRCA mutation patients whose previous treatment with platinum-based medicines led to a durable response.

At present, multiple clinical research of PARPi have been studied in BRCA1/2 mutation patients [25]. However, restricting PARPi research to BRCA1/2 mutation cancers would exclude additional cancer patients who may benefit. Hence, finding the real indications of PARPi has to be settled urgently.

Synthetic lethality and biomarkers of PARPi

Synthetic lethality is a concept where the combination of mutations in two or more genes leads to cell death, and each mutation alone is not sufficient to cause cell death. Synthetic lethal is widely used in cancer therapy to broaden the therapeutic effect for the drug. PARP detects SSB, binds to the sites of DNA nick and recruits base excision repair (BER) proteins, such as DNA-polymerase β , DNA ligase III and XRCC1. BRCA1 and BRCA2 were involved in DSB repair of DNA. PARP inhibition in BRCA1/2 mutation cancer is based on the concept of synthetic lethal strategy. It indicates that PARPi is extremely sensitive to patients with mutations in BRCA1/2 gene. In ovarian cancer, 10% to 15% women carry germline mutation of BRCA1/2. Therefore, mutation of BRCA1/2 might be a predictive factor for the effectiveness of PARPi treatment for these small subsets of patients, thus leading to the best example of personalized therapy in ovarian cancer to date. The challenge remains to develop an effective strategy to predict the biomarkers such that the patient population who

Biomarkers of PARPi for cancer therapy

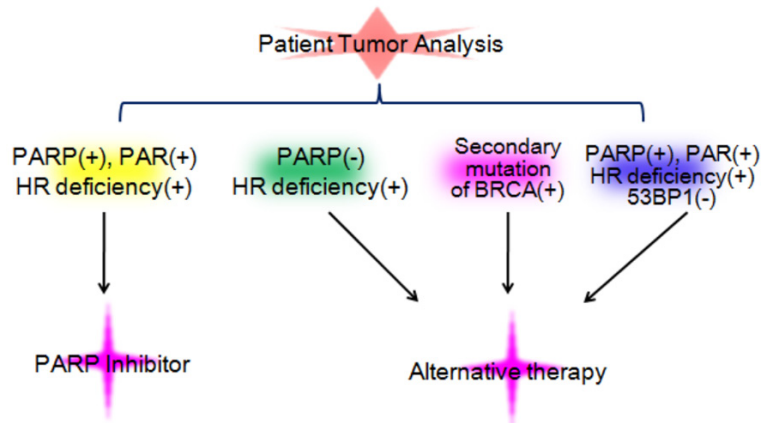


Figure 2. Biomarker system.

are more likely to respond to PARPi therapy may be identified.

Homologous recombination (HR) deficiency is a biomarker of PARP inhibitors

HR is a major pathway for the repair of DNA double-strand breaks in mammalian cells. BRCA1/2, key proteins at different stages of HR, are frequently mutated in breast and ovarian cancer. Other HR proteins, such as PTEN, ataxia-telangiectasia mutated (ATM), MRE11 and FANC, have also been identified as cancer related protein.

Konstantinopoulos et al. has proposed a BRCAness profile which contains 60 genes that can distinguish BRCA-Like from Non BRCA-like tumor with 94% accuracy [26]. However, there is no standardized method to detect BRCAness [27, 28]. PARPi, which decreases the SSB repair, increases the DSBs that require HR-mediated repair [29]. In this regard, proteins involved in HR pathway may be the biomarkers of PARPi. We review several key mutations of HR pathway and some potential biomarkers (Figure 1).

BRCA mutation

Both BRCA1 and BRCA2 gene belong to tumor suppressor gene family that precisely repair DNA in HR [30]. In 2005, both Bryant et al. and Farmer et al. found that BRCA mutant profoundly sensitizes cells to PARPi [31, 32]. Clonogenic cell survival assays demonstrated that ES cells lacking wild-type BRCA1 or BRCA2 were extremely sensitive to KU0058684 and

KU0058948, which notably enhanced 57-fold and 133-fold sensitivity. Studies by Bryant et al. showed the similar result, which specific PARPi NU1025 and AG14361 were profoundly effective at low concentration in the BRCA2-deficient cell line V-C8, as compared with V79 wild-type cell line or V-C8 cell line complemented with BRCA2 [31]. Furthermore, McCabe et al. tested KU0058684 (IC₅₀=3.2 nM) and KU0058948 (IC₅₀=3.4 nM) in CAPAN-1 cell line, which carries a naturally occurring

6174delT mutation in one BRCA2 allele accompanied by loss of the wild-type allele [33]. Wang et al. tested the potential PARP inhibitor LT-00673 in MX-1 cell line (IC₅₀=0.3 nM), which harbors BRCA-1 deficiency, and in CAPAN-1 cell line (IC₅₀=5 nM) [34].

To investigate if this sensitivity works in vivo, BRCA-deficient ES cells [32] or BRCA2-deficient V-C8 [31] cells were injected into nude mice. The result showed that significant differences in tumor formation were seen between the BRCA-deficient xenograft/drug treatment and the BRCA-deficient xenograft/vehicle treatment and also between the BRCA-deficient xenograft/drug treatment and the wild-type xenograft/drug treatment. Wang's group implanted MX-1 human mammary tumor into the flank of female nu/nu NCr mice and revealed that a potential PARP inhibitor LT673 not only reduced the cytotoxicity of cisplatin but also showed an optimistic single-agent anti-tumor activity in MX-1 xenograft model [34].

Astra Zeneca's result of Phase II study showed that Olaparib, given as monotherapy at a dose of 400 mg twice a day, has antitumour activity in carriers of BRCA-associated mutation [35]. FDA approval of Olaparib was based on a single-arm study in patients with deleterious or suspected deleterious germline BRCA-mutated advanced cancer. The percentage of Olaparib treated patients with objective response rate was 34% and the median duration of response rate was 7.9 months. The percentage with complete response was 2% and partial response was 32% [36].

A model to explain why BRCA-associated cells are extremely sensitive to PARPi by Farmers et al. [32]. They supposed that persistent single-strand gap in DNA caused by PARPi would degenerate into double strand breaks when encountered by a replication fork. In normal case, DSBs will be repaired by homologous recombination, a process in which BRCA1, BRCA2 and Rad51 are involved. With the mutation of BRCA1 and BRCA2, the replication fork will cause a persistent DNA break and result in cell apoptosis.

PTEN deficient cancer

PTEN, a tumor suppressor gene, regulates cell cycle and controls cell growth by inhibiting the PI3k/AKT pathway [37]. PTEN is frequently found to be mutated, deleted and silenced in various cancer. Recently, new findings, which PTEN involves in regulating expression of Rad51 and plays an essential role in DSBs, were demonstrated by Shen et al. [38]. Mendes-Pereira et al showed HCT116 PTEN^{-/-} cells were 20 times sensitive to KU0058948, as compared with wild type HCT116 PTEN^{+/+} cells [39]. They proposed that combining PTEN mutation with the cell that is inability to form nuclear Rad51 foci may be a biomarker in use of PARPi. It may be the result that PTEN involved in HR repair and they observed PTEN deficient human tumor cells exhibited a reduction in DSB. At the same time, they tested Olaparib (ADZ2281) undergoing clinical assessment which have an optimistic effect both compared to vehicle-treated xenografts and PTEN wild type xenografts. In clinical experiment, a 58-year-old woman, with metastatic endometrioid endometrial adenocarcinoma, was treated with Olaparib. The patient whose tumor biopsy was negative for BRCA1 and BRCA2 mutations, but displayed loss of PTEN, remained alive for 10 months after completing olaparib [40].

ATM mutation

The ATM kinase plays a critical role in DNA double strand breaks (DSBs) by phosphorylating proteins that initiate cell-cycle arrest, DNA repair [41]. The mutation of ATM gene predisposes to chronic lymphocytic leukemia (CLL), T-prolymphocytic leukemia (T-PLL), and mantle cell lymphoma (MCL) [42]. Weston et al demonstrated that PARPi Olaparib is sensitive to both chemical ATM inhibition and ATM knockdown LCL cells. However, they didn't observe differ-

ential effect of olaparib in ATM wild type [43]. Meanwhile, they also tested olaparib in vivo and generated murine xenograft models of the ATM mutant MCL cell line, Granta-519. As a result, the growth of ATM mutant Granta-519 tumor cells in a NOD/SCID xenograft model was impaired in the presence of monotherapy olaparib, both in primary lymphoid organs as well as in subcutaneous tumors. Therefore, they proposed that the primary ATM mutant leukemias may be predicted to show a differential sensitivity to PARPi.

MRE11 mutation

Repair of DNA double strand breaks, replication forks are controlled by a single protein complex, Mre11-Rad50-Nbs1 (MRN), which is activated by ATM [44]. Microsatellite instability (MSI) represents approximately 15% of colorectal cancer (CRC) [45]. MSI is caused by defective DNA mismatch repair leading to mutations such as repetitive instability located in MRE11, Rad50. Vilar et al. evaluated the PARPi ABT888 potency was five times higher on MRE11 mutant colon cancer than wild type [46]. Indeed, PARPi ABT-888 has showed a preferential activity on those MSI cell harboring mutations in both MRE11 and RAD50 genes compared to MSS cell lines (wild-type for both genes).

The FANCD1 deficiency

Fanconi anemia is an autosomal recessive condition associated with congenital abnormalities, progressive pancytopenia, and a predisposition to leukemia and solid tumor [47]. Seven of FA gene products (FANCA, FANCB, FANCE, FANCF, FANCG, FANCD1) forms FA complex that lead to monoubiquitination of FANCD2 following DNA damage. Cells with deficiency of FANCA, FANCC, FANCD2 have HR defects [48]. McCabe et al. assessed that FANCD1-deficient cells mediate sensitivity to the potent PARPi KU0058684 and KU0058948 compared with wild type cell [49].

PARP activity is a biomarker of PARP inhibitors

In 2011, PARPi stumbled in breast cancer. Paris-based Sanofi-aventis pronounced that iniparib (BSI-201) failed to prolong survival in metastatic, triple-negative breast cancer (TNBC). Then, London-based AstraZeneca announced that it wouldn't pursue phase 3 development of

its PARP inhibitor (ADZ2281) in hereditary BRCA-associated breast cancer [50]. Domagala et al. proposed that O'Shaughnessy' group started their clinical trial on the erroneous assumption that all breast cancer are PARP-positive, however, BRCA-associated cancer and triple-negative breast cancer exists low expression of PARP1 or no PARP1 expressing [51]. Whether PARP1 levels or PAR levels will predict the benefit from the use of PARPi attracted us. Loibl et al. proposed that patients with a high PARP expression showed a pCR rate of 25.7% compared to 18.8% and 6.1% in patients with medium or low expression from biopsies of 646 patients. They have suggested that cytoplasmatic PARP expression may be a biomarker for the benefit of neoadjuvant chemotherapy [52].

On the other hand, others suggested PARP activity is not regulated by the level of PARP, while it is determined by posttranslational modification or endogenous activation or repression [53]. Numerous reasons such as DNA breaks or BRCA-associated mutation [54] will have an increased PARP activity. They demonstrated that the presence of PAR polymers may be useful in identifying cancer that will respond to PARPi therapy.

In fact, we should take both the expression of PARP1 and PAR into consideration, because a large number of factors may have an impact on PARP1 activity [53]. Even if little evidence support HR deficiency results in compensatory increase in PARP levels, all the experiments in vitro were based on cell lines that exists PARP1 expression.

Resistance to PARP inhibitors

Recently clinical publications demonstrated that not all the patients would respond to PARPi. The studies from Edwards et al. provided insight into resistance to therapy caused by intragenic deletion in BRCA2 [55]. They observed that lacking a significant fraction of BRCA2 protein especially BRC repeats 6-8 and the DBD are competent in alleviating hypersensitivity of BRCA mutation cells to PARP inhibition. Sakai et al.'s data also showed that five different secondary mutations of CAPAN-1 that restored the wild type BRCA2 reading frame were resistant to both cisplatin and PARP inhibitor (AG14361) [56].

Biomarker system is proposed by us to predict potential effective patient to PARPi. Both PARP, PAR biopsy positive and HR deficiency positive patients can use PARPi. Once suffering secondary BRCA mutation, patients should choose an alternative therapy to treat.

Two other studies illustrated another mechanism of PARPi resistance in BRCA1 deficiency cell by loss of 53BP1 [57, 58]. They revealed that lack of 53BP1 enables RPA loading normally at the break site in BRCA1-deficient cells and restores the homologous recombination. Finally, loss of 53BP1 mediates the resistance of PARPi.

Potential biomarkers of PARPi for cancer therapy

As Lynparzahas been the PARP inhibitor granted a marketing authorization by both European Medicines Agency [23] and FDA [24], What is the real biomarker of PARPi has become the urgent challenge to be solved. PARP activity? HR deficiency? 53BP1? Secondary mutation of BRCA? Both in vivo and in vitro experiment demonstrated that we should not only take HR deficiency but also PARP activity into serious consideration.

In order to better predict the response of PARPi, an integrated biomarker system should be established. We proposed that the expression of PARP1, PAR and HR deficiency should be taken into consideration as a biomarker system to predict the "appropriate users" of PARPi (**Figure 2**) to help overcome the treatment failure. Discovery, replication and validation of candidate biomarker will lead to a more efficient PARPi therapy. Future studies will focus on a more convenient and effective method to predict the impact of PARPi.

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Disclosure of conflict of interest

None.

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